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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,657	DRUMM ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-13,15-23,92 and 93* is/are pending in the application.

4a) Of the above claim(s) *2,12,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-11,13,15,16,19-23,92 and 93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 2-24-07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/2/07 has been entered.

Status of Application/Amendment/Claims

Applicant's response filed 4/2/07 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 11/1/06 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 4/2/07, claims 1, 2, 4–13, 15–23, 92, and 93 are pending in the application. Claims 2, 12, 17, and 18 remain withdrawn. Claims 1, 4–11, 13, 15, 16, 19–23, 92, and 93 are currently under examination.

Domestic and Foreign Priority

Applicants' submission of an English language translation of US Provisional Application No. 60/431,173 is acknowledged. The submission was filed on 2/14/07.

However, a review of US Provisional Application No. 60/431,173 fails to find support for claims 1, 4–11, 13, 16, 19–23, 92, and 93 of the instant application, as presented on 4/2/07.

To be entitled to the benefits of 35 U.S.C. 119(e), the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/431,173 fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for instant claims 1, 4–11, 13, 16, 19–23, 92, and 93.

Specifically, no support could be found for methods of treating any eye disorder using dsRNAs of between 15 and 30 nucleotides in length (claim 1), or 20 to 25 nucleotides in length (claim 93). Furthermore, Applicants have not pointed with particularity where support can be found in the priority document for the amendments presented on 4/2/07.

Similarly, acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to EPO Application 02008761.5. However, 35 U.S.C. 112, first paragraph support for claims drawn to methods of administering dsRNAs of between 15 and 30 nucleotides or 20 to 25 nucleotides in length is not found therein.

Thus, for purposes of this examination, the earliest effective filing date of claims 1, 4–11, 13, 16, 19–23, 92, and 93 is considered to be that of PCT/EP03/04003, filed 4/16/03.

Terminal Disclaimer/Non-Statutory Double Patenting—withdrawn

The rejection of Claims 1, 3-11, 13, 15, 16, and 20-23 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 5-13, 16, 21, 44, and 47 of copending Application No. 10/511656 has been obviated by the filing of a Terminal Disclaimer. The terminal disclaimer filed on 2/14/07 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of 10/511656 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claim Objections—new

Claims 20 and 21 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 20 (not withstanding the indefiniteness, see below) recites "wherein said compound is a nucleic acid molecule or encoded by a nucleic acid molecule, and is designed to be expressed in cells of the eye." However, claim 1, from which 20 depends already requires that the composition comprise dsRNA, which is by definition a nucleic acid, and which, by definition may be encode by a nucleice acid and be expressed in any cell.

Accordingly, the claim appears to broaden the scope, and is, at the same time, unnecessarily duplicative.

Correction is required.

Claim 21 recites "wherein the composition is in a form designed to be introduced into the cells or tissue of the eye by a suitable carrier, characterized by the application occurring outside the blood-retina barrier." However, claim 1 from which 21 depends, already requires administration of a composition outside the blood-brain barrier. For the method of claim 1 to be enabled, it goes without saying that the composition of claim 1 is in a form to be introduced into the cells of the eye by a "suitable" carrier for administration outside the blood-retina barrier. No other form or carrier is possible. Moreover, characterizing the application as occurring outside the blood-retina barrier does not further define or narrow the method claimed in claim 1.

The claim, claim 21, is unnecessarily redundant and duplicative. Thus, Claim 21 is also objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112—new

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4–11, 13, 15, 16, 19–23, 92, and 93 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as follows.

Claim 1 is rejected because the claim requires administering "a composition comprising a dsRNA" but does not define any other components present in the composition. By definition, a

composition is a "product of mixing or combining various elements or ingredients" (Merriam-Webster Dictionary online). Thus, a composition comprises at least two components. However, claim 1 defines only one component: dsRNA. Moreover, claims 8, 21, 22, and 23, which specifically require a composition designed for a particular mode of delivery, similarly fail to define the additional components necessary to fulfill these properties. While it is acceptable to define a component according to its function, the specification fails to provide explicit definitions of these particular types of compositions such that one of skill would appreciate the metes and bounds of the claims. Thus, the claim fails to particularly point out and distinctly claim the subject matter which the applicant regards as his invention, rendering the metes and bounds of the claim as a whole unclear. Dependent claims 4–11, 13, 15, 16, 19–23, 92, and 93 are rejected therefor.

***

Claims 8, 21, 22, and 23 require administering a composition that "is in a form designed to be applied outside the retinal region of the blood-retina barrier", "in a form designed to be introduced into the cells or tissue of the eye by a suitable carrier", "in a form designed for systemic administration or for administration by iontophoresis", and "designed for retrobulbar application."

The scope and meaning of the limitation "a form designed to be applied outside the retinal region of the blood-retina barrier" is defined neither by the claims or the specification in a manner that would adequately apprise one of skill as to which compositions are specifically included or excluded by the claims. As a result, the metes and bounds of the claims as a whole are unclear. For example, the specification does not enable one of skill to distinguish between

compositions designed to be applied outside the barrier from those not designed to be applied outside the barrier or from those designed to be applied inside the barrier. The specific differences and distinguishing characteristics are not defined. As a result, it is unclear how the subject matter of claim 8 is specifically distinguished from that of claim 1, from which it depends.

Similarly, Claim 21, which requires a composition "in a form designed to be introduced into the cells or tissue of the eye by a suitable carrier" is indefinite since it is unclear how such compositions may be distinguished from all other compositions.

Correction is required.

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Claims 9–11, 13, 20, and 21 are rejected as being indefinite because of the recitation "said compound" (9 and 20), "said antagonist/inhibitor" (11), and "the application" (21). There is insufficient antecedent basis for these limitations in the claims.

With regard to "said antagonist/inhibitor" the preceding claim, claim 9, recites "inhibitor/antagonist." It is unclear whether the recitations are identical. Moreover it exceptionally unclear why both words are needed or required, given that claim 1 is drawn to a dsRNA that modulates a gene. The terms appear to be redundant and it is unclear whether the claim specifically requires an inhibitor or antagonist or both, or even how one would of skill would differentiate between the two.

If the terms inhibitor and antagonist have overlapping but non identical meanings, as appears to be the case from the definitions at paragraphs 65 and 66 of the instant application publication, the claims remain indefinite because it is unclear whether applicant is claiming an

inhibitor or an antagonist and it is unclear from the specification whether the scope of the terms is the same or different.

Correction is required.

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Claim 11 is further rejected as being indefinite because of the recitation "derived from." Neither the claim nor the specification explicitly defines the limitation so as to apprise one of skill as to which structures are specifically included or excluded by the claims because the specification has not clearly defined how and to what degree a compound can differ from the claimed nucleic acids and still be considered a derivative.

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Claim 13 is further rejected as being indefinite because of the recitation "substantially consists of ribonucleotides." Given that "consists of" is a term of art used to define the scope of the claim (MPEP 2111.03), it is unclear how or whether the modifier "substantially" changes the scope of the claim. It is not even clear whether "substantially consists of" is closed, open, or partially closed language. Further confusing interpretation of the claim is the fact that the claim depends from a claim drawn to a method of administering dsRNA. It goes without saying that dsRNA "substantially consists of ribonucleotides." The limitation in claim 13 casts doubt on the definition of the term "ribonucleotides."

Correction is required in all cases.

Claim Rejections - 35 USC § 112, first paragraph—new

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following rejection substantially reiterates the previous rejection under this section for lack of written description, but includes new grounds not previously addressed. Applicants' arguments in response to the previous rejection under this section will be addressed below as they pertain to the instant rejection.

Claims 1, 4–11, 13, 15, 16, 20–23, 92, and 93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed

invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claims are drawn to methods for treating disorders of the eye, specifically including disorders related to angiogenesis, neovascularization, retinal pigment epithelium, neurosensory retina, choriodea, wet age-related macular degeneration (AMD, and diabetic retinopathy comprising administering a composition comprising a dsRNA capable of modulating a target gene.

Claims 8 and 21–23 specifically require that a composition in a form designed for application outside the blood-retina barrier, such as by eye drops, retrobulbar application, systemic or iontophorectic administration.

Adequate written description support does not exist in the instant application for all these methods because neither the instant application nor the prior art adequately describe a representative number of target genes, the abnormal expression of which has been clearly correlated with the countless number of eye disorders embraced by the claims nor adequately describe the particular features or distinguishing characteristics common to genes that are related to or correlated with the multitude of eye disorders treatable by the instant methods. As a result, Applicants have not described the target genes to be targeted by the instant methods using inhibitory dsRNA. Logically, if neither the instant application nor the prior art enables one of skill in the art to instantly recognize the genes to be targeted by the instant methods, Applicants have not described the genus of dsRNAs necessary to treat all the disorders embraced by the claims. Therefore, Applicants have not demonstrated they were in possession of the genus of methods now claimed.

Additionally, adequate written description support does not exist for the methods now claimed in instant claims 8 and 21–23 because neither the instant application nor the prior art adequately describes a sufficient number of compositions nor provides any description of the features or makeup common to the genus of compositions designed to be applied outside the blood-retina barrier, systemic or iontophoretic administration, or retrobulbar application for treatment of the disorders now embraced by the claims. Neither the particular content nor the general structural properties of these particular compositions are described in the application in a manner that would enable one of skill in the art to recognize Applicants were in possession of all such compositions. Put another way, neither the application nor the prior art provides any description that would enable one of skill to distinguish the instantly recited compositions from any other composition designed for any other purpose or mode of delivery.

Thus, the claims are extremely broad. The claims encompass a large genus of methods requiring a multitude of distinct dsRNA compounds for modulating (inhibiting or upregulating) any gene in any species associated with any disorder of the eye, and in more narrow embodiments, any of the specific classes of disorders recited in claims 5 and 6.

Moreover, Applicant claim a genus of compositions designed for the particular purpose of delivery outside the blood-retina barrier without specifically describing what those compositions look like. In this sense, Applicants are essentially inviting the skilled artisan to experiment and identify such compositions empirically. It is clear that the compositions needed to practice the instant methods must be suitable for delivery outside the blood-retina barrier, but Applicants have not described the particular features or properties common to those compositions. The Examiner notes the disclosure at paragraph 50 of the instant application

publication; however this disclosure does not address the particular features of the compositions claimed in claim 23, for example.

With regard to the target genes and dsRNAs needed to modulate such genes for the treatment of any eye disorder, the Examiner is unable to readily find any disclosure in the instant application or prior art nor any evidence in the case record establishing the correlation between a representative number of target genes and the treatement of the genus of eye disorders, wherein the target gene is of particular relevance to angiogenesis, neovascularization, RPE, choroids, AMD, and diabetic retinopathy in the eye. Such disorders are expected to involve a complex array of genes and genetic factors. While paragraph 59 of the instant application points to a possible genetic element in AMD, the specification fails to identify the gene(s) responsible or provide any guidance as to which genes in particular should be targeted to treat AMD.

As a result, one of skill in the art would be left to de novo trial and error experimentation to identify such genes to practice the instant method. One of skill would therefore not recognize that Applicants were in possession of the genus of methods now claimed at the time of filing.

The dsRNAs required for the methods are recited in terms of their function only, there is no art-recognized correlation between their structure and their required function (treatment of eye disorders), and the specification does not provide the support needed to enable one skilled in the art to predict with a reasonable degree of confidence the structure of the dsRNAs from a recitation of function alone. What is needed is a description of the target genes that have been clearly correlated with the eye disorders that may be treated by the instantly claimed methods.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.

A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations." (Tronzo v. Biomet Inc., 156 F.3d 1154, 1158, 47 USPQ2d 1829, 1832 [Fed. Cir. 1998]).

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

MPEP 2163 states in part that "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. >The disclosure of only one species encompassed within a genus adequately describes a

claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

In the instant case, applicants have not satisfied either of these criteria. That is, the instant application discloses no correlation between the structures of the genus of target genes and the genus of eye disorders. Thus, Applicant has not demonstrated possession of the genus of dsRNAs needed to practice the instant methods.

Further, Applicants have not demonstrated possession of the genus of compositions designed particularly for the mode of administration now required because Applicants have not described the features distinguishing such compositions from all other compositions. The compositions are claimed in terms of their intended uses only with no description of how the intended use relates to the physical and chemical characteristics of the compositions themselves.

As regards the target genes and dsRNAs necessary to inhibit the expression of such genes, while the specification and prior art adequately describes one exemplary target gene for the treatment of excessive angiogenesis, VEGF, and one target gene for the treatment of an eye disorder in general, SEQ ID NO:3 (claim 19), evidence is not found clearly establishing a link between any other genes and the disorders now embraced, wherein applicant may clearly envision the structure of the dsRNAs needed to treat that disorder.

Apart from GFP, and the gene targets SEQ ID NO:1, 2, and 3 (see page 18 of specification as originally filed), a review of the specification fails to find any description, by words, structures, figures, diagrams, or formulas, of a representative number of dsRNA species

nor any feature common to the genus that may be used in the instant methods to treat any CNS or eye-related disorder. While the specification teaches at pages 52-54 that dsRNA targeting GFP may be delivered to the retina of a transgenic mouse via intravenous injection and that GFP expression in the retina may be reduced by systemic delivery in a mouse, this example is not directed to the treatment of any eye or CNS disorder and does not describe any dsRNA or siRNA or any vector thereof, nor any other molecule for use in the instant methods to treat an eye or CNS disorder. And while pages 55-58 list several genes, there is no disclosure explaining the relevance of these genes to any particular disorder nor any description of the compounds that are to be used to inhibit or agonize these genes so as to provide a definitive treatment effect. While these genes may indeed be suitable targets for a given disorder, even if one knew which gene was related to any given disorder and whether or not to inhibit or agonize the gene or gene product, one of skill in the art would, nevertheless, be left to de novo screening methods to identify the dsRNAs having the desired activity to produce the desired therapeutic effect.

MPEP §2163 states, in part: "[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)."

As taught by Weber et al. (previously cited), page 6264, "Mutations in any one of the many genes involved in the complex biochemistry of the eye could theoretically impair vision."

Applicants have not described which genes of the many possible are specifically linked to the disorders treatable by the instant methods, which treat disorders by inhibiting the expression of a gene.

Accordingly, only methods comprising the use of dsRNAs targeted to SEQ ID NO:3 and VEGF meet the written description requirement.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Response to Arguments

Applicants have argued, in response to the previous rejection under this section (Remarks filed 4/2/07, page 6) that there is no confusion over the metes and bounds of the claims, that Applicant has provided specific structural and functional guidance for the dsRNA that enables one ordinary skill in the art to envision the genus of compounds that may be administered outside the blood-retina barrier, that Applicant has demonstrated the ability to target eGFP in the retinal pigment epithelium (RPE) by systemic administration.

Applicant's arguments filed have been fully considered but are not persuasive.

With regard to the metes and bounds of the claims, this is not an inquiry addressed by the instant rejection. Such questions are more properly addressed under 35 USC §112, second paragraph, as set forth above.

Applicants argue that they have provided sufficient description of the genus of dsRNAs needed to practice the methods, but provide no evidence of such description, nor do applicants point with particularity where such description may be found in the instant specification or the prior art.

The Examiner notes that "Information which is well known in the art need not be described in detail in the specification. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986)" (MPEP §2163). Therefore, it would be helpful towards overcoming the instant rejection if Applicants could point with particularity to evidence in the specification or the prior art showing a correlation between the abnormal or aberrant expression of a representative number of target genes and a representave number of eye disorders, including those specifically related to or caused by the conditions recited in claims 5 and 6.

With regard to Applicant's assertion that the disclosure enables one of skill to deliver the genus of dsRNAs across the blood-retina barrier, the Examiner agrees. However, the instant rejection is not for lack of enablement. Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc.* v. *Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

The instant rejection has nothing to do with whether one can deliver dsRNAs to inhibit eGFP in the eye.

Rather the instant rejection addresses the lack of written description of the correlation between a representative number of eye disorders and a representative number of abnormally

expressed genes recognized as being associated with such disorders. Such information is necessary to describe the dsRNAs needed to practice the full scope of the methods now claimed.

Accordingly, the instant claims remain rejected for lack of written description support.

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Claims 1, 4–11, 13, 15, 16, 19–23, 92, and 93 are also rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting the expression of a gene in the eye using a dsRNA, and for treating an eye disorder associated with the expression of SEQ ID NO:3 and VEGF, does not reasonably provide enablement for methods of increasing the expression of any gene in the eye using a dsRNA, or treating any eye disorder by targeting any gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

Independent claim 1, from which all other claims depend, directly or indirectly, claims a method for treating an eye disorder by administering a dsRNA capable of modulating a target gene.

Broadest reasonable interpretation of the term "modulating" as used therein embraces methods for both "increasing" and "decreasing" the expression of a target gene.

Furthermore, because claim 1 does not include the term "expression of" before the term "a target gene" in line 4, but states only "modulating a target gene," the claim may be interpreted to include methods of modulating a target gene by other mechanisms such as regulating promoter activity.

In view of the breadth of the claims in combination with the fact that the specification (page 14) discloses using the dsRNA compositions for treating a multitude of different eye disorders by "modulating a target gene" (page 7-8), requires that these claims be evaluated to determine whether the specification provides teaches how to use these compositions for treating these conditions by modulating, i.e., increasing and decreasing, the expression of a target gene, or by influencing the activity of the gene by some other mechanism.

As a corollary, the breadth of the claims requires evaluating the specification for enabling disclosure teaching one of skill how to use dsRNAs to inhibit the expression of a gene to treat the complete genus of disorders now embraced by the claims. That is, it is imperative that the specification or the prior art have taught one of skill at the time of filing how to correct the genus

of eye disorders by inhibiting the expression of specific genes, gene families, or classes, which may be overexpressed or expressed as mutant isoforms sensitive to the effects of interference by dsRNA. One of skill would have needed to know which genes to target in order to effectively treat the disorder without undue experimentation.

However comprehensive disclosure enabling one of skill to practice the full scope of the instant methods without undue experimentation is lacking.

While the instant application provides working examples teaching one of skill how to deliver dsRNA to into cells in the eye of subject to inhibit the expression of a target gene in the cell by post-transcriptional gene silencing, the instant application fails to provide any disclosure showing how the administration of dsRNA may increase the expression of a gene in a cell in the eye, nor how a dsRNA may modulate the activity of a promoter in vivo. All of which are embraced by the limitation "capable of modulating a target gene" in claim 1.

Further, a review of the prior art fails to find any evidence that dsRNAs of 15 to 30 nucleotides may specifically increase the expression or activity of a gene to treat an eye disorder.

Given the absence of such disclosure, the skilled artisan would not know *a priori* whether introduction of dsRNAs *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the agent reaching the proper cell in a sufficient concentration and remaining for a sufficient time to increase the expression of a target gene. Neither the specification nor the prior art provide the guidance necessary to teach one of skill how to increase the expression of a gene using dsRNA, and there is no evidence in the prior art or specification to even suggest that dsRNA is capable of such activities. Rather, a careful reading of the specification shows that applicant's invention is directed to the inhibition of gene expression not enhancing gene

expression. The latter is conventionally accomplished by expressing the full length gene not by administering short interfering RNA.

Additionally, neither the prior art nor the specification enable one of skill to practice the full scope of the methods now claimed without undue experimentation, because the specification does not teach the genus of genes specifically overexpressed or aberrantly expressed, i.e., as mutant isoforms in the complete genus of eye disorders, and how such expression is specifically related to the eye disorders embraced by and specifically recited in the instant claims. Such information is essential to the practice of the instant methods. While the specification provides enabling disclosure for delivering dsRNA into the eye by administration outside the blood-retina barrier, the specification is not considered to be enabling for treating all possible eye disorders. Given the complexity of the biochemistry of such disorders and the many genes expressed in the eye which may or may not be directly related to the disorders, one of skill would require specific guidance as to how to design the dsRNAs effective for inhibiting the expression of a gene involved in any disorder in order to treat the disorder. Such comprehensive disclosure is lacking.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement. Replacing the "modulating" language with "inhibiting" language in the instant

claims, and inserting terminology to clearly indicate that the dsRNA inhibits target gene expression, would overcome this rejection.

Claim Rejections - 35 USC § 102—new

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4, 6–11, 13, 15, 16, 20, 21, 22, 23, 92, and 93 are rejected under 35 U.S.C. 102(e) as being anticipated by King et al. (US 2002/0165158 A1).

King et al. taught methods for making and using siRNA targeted to PKCβ to treat angiogenesis-related disorders, including diabetic retinopathy and other neovascular disorders of the eye (page 1, 8, 10, and 11, for example). It is taught that the agent [the PKCβ antagonist] may be administered to the eye, e.g., as aqueous eye drops or in a cream, lotion or other vehicle suitable for administration onto the eye surface (paragraph 125, page 10), systemically, or transmucosally (paragraph 190). Additionally, it is said that the pharmaceutical composition may be administered directly into a retinal tissue, arthritic tissue, or tumor tissue of the subject (paragraph 194). Several types and forms of compositions are described (page 10).

Accordingly, King et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103—New

Claims 1, 4-11, 13, 15, 16, 19–23, 92, and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson et al. (US Patent 5,814,620); Dryja et al. (US Patent 5,498,521), Weber et al. (1991) *Nucleic Acids Res.* 19:6263-6268; Epstein (1998) *Methods: A Companion to Methods in Enzymology* 14:21-33; Collins et al. (1992) "The human beta-subunit of rod photoreceptor cGMP phosphodiesterase: complete retinal cDNA sequence and evidence for expression in brain" *Genomics* 13 (3): 698-704; and Tuschl et al. (US Patent Application 2004/0259247 A1); Bass (2001) *Nature* 411:428-9.

The instant rejection is new to the extent that Tuschl et al. has been substituted for Elbashir et al., as it is considered to be a more expansive and all encompassing disclosure with regard to the methods, materials, benefits, and utilities of siRNAs.

Finally, Collins et al. has been added to the rejection as further evidence establishing the link and providing the motivation to target cGMP phosphodiesterase (SEQ ID NO:3) as a method for treating eye disease.

Applicant's arguments in response to the previous rejection will be addressed below as thy pertain to the instant rejection.

Applicants are further advised that the limitations set forth in claims 8, 21-23, and 92 further defining the properties of the composition used in the instant methods, do not limit the method to any particular form of administration. Rather the claims speak only to the nature of the composition used in the method not to the route of delivery. The claims as a whole require only

that the administration be outside the blood-retina barrier. Systemic administration is within the scope of the claims, as are eye drops. For example, claim 23 does not require retrobulbar administration only that the composition be formulated for such. Given the lack of disclosure teaching what such compositions are specifically composed of or how such compositions differ from those disclosed in the prior art, compositions disclosed in the prior art cited herein are considered to be such compositions.

Moreover, the Examiner notes that Claim 1 recites the phrase "capable of modulating a target gene." It has been held that the recitation that an element is "capable of" performing a function is not a positive limitation but only requires the ability to so perform. *In re Hutchison,* 69 USPQ 138, 141.

Robinson et al. taught a method for treating diabetic retinopathy and macular degeneration comprising the step of administering to a subject afflicted with diabetic retinopathy a therapeutic amount of an antisense oligonucleotide specific for vascular endothelial growth factor nucleic acid and effective in inhibiting the expression of vascular endothelial growth factor in the retina, including choroidal neovascularization (claim 1 and Examples 4 and 5, column 15, for example). Several representative embodiments of anti-VEGF oligonucleotides are disclosed at Table 1, column 6). The antisense oligonucleotide may be composed of ribonucleotides, deoxyribonucleotides, or a combination thereof (column 7, lines 30-35; claim 5). They may be combined with a variety of pharmaceutically acceptable carriers and formulated in pyrogen-free compositions in a way suitable for intraocular, intravitreal, or systemic administration (column 10, lines 20-40; column 11, lines 5-15). It is said the antisense

oligonucleotide may be formulated as a sterile, buffered, isotonic solution (column 10, lines 20-35).

Robinson et al. further teach methods for delivering antisense oligonucleotides intraocularly to cells in the eye to treat diseases associated with the eye. Robinson et al. teach specifically methods for targeting VEGF in retinal cells using several forms of administration

For example, Robinson et al. taught that "Intravitreal injections of oligonucleotides against VEGF can be an effective means of inhibiting retinal neovascularization in an acute situation. However for long term therapy over a period of years, systemic delivery (intraperitoneal, intramuscular, subcutaneous, intravenous) either with carriers such as saline, slow release polymers, or liposomes should be considered" (column 11). Similarly at columns 9 and 10, Robinson et al. taught that the synthetic oligonucleotide could be administered by intraocular, oral ingestion, inhalation, or cutaneous, subcutaneous, intramuscular, or intravenous injection.

Thus, Robinson taught systemic administration, which is considered to be outside the blood-retina barrier, as evidenced by claim 22.

While Robinson et al. taught methods and materials making and using antisense oligonucleotides to treat eye diseases, including those recited in the claims, Robinson et al. do not teach dsRNAs or siRNAs for modulating genes associated with eye disease or antisense or dsRNAs specifically targeted SEQ ID NO:3.

Nevertheless, SEQ ID NO:3 is shown in the prior art, and its correlation to eye disorders is well established.

With regard SEQ ID NO:3, the instant application teaches that SEQ ID NO:3 corresponds to the beta-subunit of rod cGMP phosphodiesterase corresponding to GenBank Accession No. NM_000283 (page 18), which is 3283 nucleotides in length. A standard search of SEQ ID NO:3 finds that SEQ ID NO:3 corresponds to GenBank Accession No. S41458, which is 3231 nucleotides in length (see search result in Exhibit A, provided with the Action of 7-12-06). A comparison of NM_000283 and S41458 shows that NM_000283 comprises S41458 (compare Exhibits B and C, provided with the Action of 7-12-06).

Weber et al. teach the full length sequence of rod cGMP phosphodiesterase corresponding to GenBank Accession No. NM_000283 (See Exhibit C, provided with Action of 7-12-06). Weber et al. also expressly taught a link between cGMP phosphodiesterase and retinal degeneration in the rd mouse, and states that any one of the many genes involved in the complex biochemistry of the eye could theoretically impair vision, and that few forms of human hereditary retinal degeneration such as gyrate atrophy of the choroid and retina, choroideraemia, and autosomal dominant retinitis pigmentosa have been linked to mutations in specific genes (page 6264).

Dryja et al. teach methods diagnosing in a mammal, e.g., a human subject, an increased likelihood of, inclination toward, or susceptibility to developing a disease, e.g., retinitis pigmentosa, in which a mutant form of a human photoreceptor protein is a causative agent. Human photoreceptor proteins said to be potential causative agents include the beta subunit of rod retinal cGMP phosphodiesterase (column 2, top). Dryja et al. teach that mutant photoreceptor proteins such as cGMP phosphodiesterase may be involved in hereditary retinal degenerative

diseases in which progressive, bilateral degeneration of retinal structures leads to loss of retinal function; these diseases include, for example, age-related macular degeneration (column 1).

In an exemplary embodiment, Dryja et al. teach antisense probes that may be used to diagnose the presence and relative quantity of the beta subunit of rod retinal cGMP phosphodiesterase corresponding to the gene disclosed by Weber et al. (see Example 9, column 15, lines 35-45), which, as explained above, also corresponds to SEQ ID NO:3. It was found that patients with mutations in the PDE .beta. gene had clinical findings typical of retinitis pigmentosa (column 17, top). Accordingly, Dryja et al. suggest that the expression of a mutant form of the protein encoded by SEQ ID NO:3 is associated with a disorder of the eye.

Epstein et al. teach the use of antisense inhibitors for specifically regulating phosphodiesterase genes, both *in vitro* and *in vivo*. It is taught for example that the goal of antisense technology is to develop small oligonucleotides, plasmids, or retroviral vectors that can be introduced into cells in order to inhibit gene products specifically. Epstein et al. teach that antisense oligos can be used to inhibit essentially any isoform of PDE (page 21). Epstein et al. provide a complete blueprint for the design and preparation of antisense oligonucleotides against the known PDE gene sequences (see pages 22-25). Epstein et al. state that a number of excellent reviews have been written recently that describe the characteristics of the different PDE isoforms, their regulation, function, and progress in development of pharmacological inhibitors of PDE as therapeutic agents (page 21, 2nd column). Epstein et al. cite a number of additional references as support therein.

Collins et al. echos and reinforces the disclosures of Dryja et al. and Epstein et al., teaching the full length cDNA sequence of rod cGMP phosphodiesterase, which is found to be

100% identical to instant SEQ ID NO:3, now recited in claim 19. Collins et al. state that the molecular cloning of the cDNA encoding for the PDEB represents the first step in establishing whether this gene plays a causative role in any one of the several human hereditary retinopathies.

Tuschl et al. teach short double-stranded RNA molecules for mediating target-specific gene silencing via RNA interference (RNAi) in human cells (paragraphs 10, for example). It is taught that double-stranded RNA molecules 19-25 nucleotides in length have RNAi activity and may trigger the specific degradation of homologous RNAs within the region of identity with the dsRNA (paragraphs 5, 7, 11, and 17 for example). Tuschl et al. teach that siRNA duplexes are preferably composed of 21-nt antisense siRNAs and should be selected to form a 19-bp double helix with 2-nt 3' overhanging ends (paragraphs 9, 11, 179).

In summary, the Tuschl et al. reference is considered to be a complete blueprint for the design, synthesis, and use of short interfering, double-stranded RNA, in modified or unmodified forms, against any desired target gene. The reference contains detailed descriptions and several examples typifying the use of siRNA in cell culture, and the Application Publication expressly suggests the use of siRNA *in vivo* for use in therapeutic and clinical settings (paragraphs 31-36).

Importantly, Tuschl et al. also compare siRNA methodology to that of antisense and ribozyme techniques for inhibiting gene expression. At paragraph 148, for example, Tuschl et al. state that siRNAs are extraordinarily powerful reagents for mediating gene silencing and that siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments. At paragraph 137, Tusch et al. state that the remarkable finding that synthetic 21 and 22 nt siRNA duplexes can be used for efficient mRNA degradation provides new tools for sequence-specific

regulation of gene expression in functional genomics as well as biomedical studies. The siRNAs may be effective in mammalian systems where long dsRNAs cannot be used due to the activation of the PKR response. As such, the siRNA duplexes represent a new alternative to antisense or ribozyme therapeutics.

Bass teaches that, like some antisense oligonucleotides, which trigger RNase H-catalyzed cleavage of their targets, siRNAs trigger the degradation of complementary messenger RNAs (page 428 and Fig. 1). A general outline of the RNAi mechanism is taught, showing how siRNA-mediated RNAi may be used to interfere with gene expression using siRNAs directed against specific mRNA sequences (Fig. 1). Bass teaches that RNAi has repeatedly proven itself to be more robust that antisense techniques: it works more often, and typically decreases expression of a gene to lower levels, or eliminates it entirely. Furthermore, siRNAs are effective at concentrations that are several orders of magnitude below the concentrations typically used in antisense experiments.

Thus, the prior art teaches, in general, that siRNAs and antisense oligonucleotides can be used to produce the same effect, albeit with different potencies and by different biochemical mechanisms. siRNAs and antisense oligos can both be used to inhibit gene expression *in vivo* or *in vitro*, via mRNA degradation or translation attenuation, and, thus, both types of nucleic acids may be used to prevent the expression of a gene in a cell. For example, Bass teaches that antisense RNA is another technique to prevent the expression of particular genes (page 429). Thus, in this sense, siRNAs and antisense oligos are art-recognized equivalents that may be used for the same purpose: reducing or inhibiting gene expression. (See for example MPEP §2144.06, SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE.)

Nevertheless, as explained above, siRNAs possess certain advantages over antisense oligos, which would motivate one of ordinary skill in the art to select siRNAs over antisense oligos to more efficiently block and/or reduce the expression of any given target gene, particularly a gene known to be involved in cancer.

Therefore, it would have been obvious to one of ordinary skill in the art, at the time the invention was made, to make and use siRNAs, as taught by Tuschl et al. and Bass, targeted to VEGF mRNA and SEQ ID NO:3, corresponding to beta subunit of rod cGMP phosphodiesterase, to inhibit the expression of VEGF and mutant isoforms of SEQ ID NO:3 and consequent development of ocular diseases associated with the expression of VEGF and mutant isoforms of SEQ ID NO:3, as taught by Robinson et al. Weber et al., and Dryga et al. Further, it would have been obvious to administer said siRNAs by any number of means including systemically, as taught by Robinson et al. It would further have been obvious to apply the siRNAs directly to the area affected by the disease—the eye—by direct application, injection, or topically, as by eye drops. There is nothing in the art nor any evidence of record showing any express teaching away from the use of eye drops for the administration of any oligonucleotide-based therapeutic. It is a matter of common sense to apply the therapeutic agent directly to the area of treatment.

One would have been both well motivated and have had a reasonable expectation of success given that Dryja et al. teach that mutant isoforms of beta phosphodiesterase (i.e., SEQ ID NO:3) may predispose individuals to macular degeneration, and given that Robinson et al. teach that antisense compounds may be used effectively in retinal cells specifically to inhibit the expression of genes associated with macular degeneration, and given that Epstein teaches that

antisense compounds may be used effectively to inhibit the expression of phosphodiesterases in particular. Given that Tuschl et al. and Bass teach that siRNAs are in general more potent than antisense oligonucleotides for reducing gene expression in cells, one of skill would have been motivated to substitute siRNAs for antisense oligonucleotides in the methods of Dryja et al. and/or Epstein et al. to silence the expression of genes such as SEQ ID NO:3 associated with eye disorders.

One would have had a reasonable expectation of success in targeting mutant forms of SEQ ID NO:3 as well as SEQ ID NO:3 itself given that Dryja et al. together with Collins et al. teach both the wild type form, as disclosed in Weber et al., and common mutations thereof leading to eye-related disease (see example 9).

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

In response to the previous rejection under this section, Applicants have argued that the cited references do not teach administration of antisense or dsRNA outside the blood-retina barrier. Applicants argue that Robinson et al. teach away from such administration by teaching intravitreal injection. Applicants argue that the references do little more than teach *in vitro* applications. Applicants argue that one of skill would not have been motivated to treat eye disease by administering antisense or dsRNA outside the blood-retina barrier. Applicants appear to contend that disclosure in Bass that siRNA use in vitro is problematic discredits or

discourages the use of siRNA in vivo, and that the combination of references does not provide a reasonable expectation of success.

Applicant's arguments filed 4/2/07 have been fully considered but are not persuasive.

The Examiner respectfully disagrees with Applicant's characterization of Robinson et al. and Bass. Robinson et al. does not teach away from any form of administration. Robinson et al. in fact teach several alternatives, including systemic and intravitreal injection. Applicants are specifically referred to columns 9-11, wherein these modes of delivery are discussed.

"[T]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed...." *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). MPEP 2141.02

Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. MPEP 2123.

For these same reasons, and given that the use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned---they are part of the literature of the art, relevant for all they contain---one of skill would have been motivated to try a number of different delivery methods including systemic and topical delivery. Given that the prior art taught several modes of administration of antisense oligos for treating eye disease, and that eye disease caused by abnormal gene expression was amenable to in vivo delivery of antisense oligos, and given that Tuschl et al. and Bass both encouraged the use of siRNAs in mammals for both in vitro studies and in vivo therapy,

motivation is clear. There is absolutely no evidence to suggest one of skill would be discouraged from using siRNA to treat eye disease.

Applicants provide no evidence that the prior art specifically taught away from administering antisense outside the blood retina barrier.

Rather, Applicants appear to argue that the discovery that dsRNA is inherently able to cross the blood-retina barrier is evidence of patentability. However, as MPEP 2112 explains, "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

The fact that the prior art did not appreciate or recognize that dsRNA readily passed through the blood-retina barrier is of no consequence, absent evidence that one of skill would have been expressly discouraged from administering antisense or dsRNA outside the blood retina barrier for the treatment of eye disease. See MPEP 2112.

See also MPEP 2144.09, which states in part that "However, a claimed compound may be obvious because it was suggested by, or structurally similar to, a prior art compound even though a particular benefit of the claimed compound asserted by patentee is not expressly disclosed in the prior art. It is the differences in fact in their respective properties which are determinative of nonobviousness. If the prior art compound does in fact possess a particular benefit, even though the benefit is not recognized in the prior art, applicant's recognition of the

benefit is not in itself sufficient to distinguish the claimed compound from the prior art. *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991)."

Applicants will note that the rationale for combining the cited prior art teachings does not rely on the recognition of the undisclosed property of crossing the blood-retina barrier without the need for delivery enhancing vehicles, but on the fact that the prior art taught that eye disorders may be treated by administering antisense, and that siRNAs are functionally equivalent to but much more potent than antisense oligos. There is reason to suggest one of skill would be motivated to use siRNAs in place of antisense in the methods of Robinson et al. for example.

Response to Applicants' Arguments

Applicants' arguments presented on 4/2/07 not specifically addressed above are considered to be moot in view of Applicants' amendments to the claims and in view of the new and/or reiterated rejections stated herein, above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Louis V. Wollenberger, Ph.D.
Examiner
Art Unit 1635

May 10, 2007

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